REMARKS

Claims 23, 39-41, 44, 46, and 50-57 are pending in the application. Claims 45, 47, 52, and 53 are withdrawn from consideration at this time as a result of a species election, and may be examined in this application pending the outcome of the examination of the elected species.

The amendment of claim 23, 29, and 41 are supported by disclosure throughout the specification, e.g., at page 37, line 27, to page 35, line 6; and page 42, line 28, to page 47, line 25. Support for new claims 54-57 and further support for amended claims 23, 29, and 41 is provided at page 48, line 27, to page 52, line 14, of the specification.

Informalities in the disclosure have been corrected as follows. The specification has been amended to clarify that HAAH polypeptide refers to the amino acid sequence of SEQ ID NO:2 and HAAH cDNA refers to the nucleotide sequence of SEQ ID NO3. The specification has also been amended to insert a reference to a sequence (SEQ ID NO:2) on page 6, line 16, of the specification.

The claims have further been amended to insert sequence identifiers.

With respect to the Declaration/ Power of Attorney, co-inventor, Dr. Carlson, has initialed and dated the correction of his home address. An initialed/dated copy of the Combined Declaration and Power of Attorney document is submitted herewith.

No new matter has been added.

I. Rejections under 35 U.S.C. § 112, second paragraph

Claims 23-25, 39-44, 46, and 48-51 were rejected for indefiniteness for recitation of the claim terms "HAAH" and "IRS". The claims have been amended to add sequence identifiers (SEQ ID NO:2, HAAH; and SEQ ID NO:5, IRS-1) as suggested by the Examiner.

Claim 40 was rejected for indefiniteness for recitation of the claim term "EB1089". The Examiner stated: "EB1089 is a trade name; the compound represented by EB1089 can be altered with time." Contrary to the Examiner's statement, the designation "EB1089" is not simply a tradename, but an art-recognized designation of a specific chemical compound (see record from Chemical Abstracts Registry listing record for EB1089; Attachment A). As evidenced by the Registry listing, the meaning of the term is not variable, but is a precise term that identifies a compound with particularity.

Withdrawal of this rejection is therefore requested.

II. Rejections under 35 U.S.C. § 112, first paragraph

Claims 23-25, 39-44, 46, and 48-51 were rejected for overbreadth.

In item 9 of the Office Action, the Examiner states:

> the specification, while being enabling for a method of inhibiting tumor growth in a mammal comprising the administration of a druge which is internalized by said tumor cell wheein said drug inhibits or blocks the tyrosine phosphorylation of IRS-1, or a method of inhibting tumor growth in a mammal comprising the expression of dominant-negative mutants of IRS-1 wherein dominant negative mutants inhibit the phosphorylation of tyrosines on IRS-1, does not reasonably provide enablement for a method of inhibiting tumor growth comprising administration of a compound which inhibits signal transduction through the IRS pathway by means other than inhibiting phosphorylation of IRS-1, or a method of inhibiting tumor growth in a mammal comprising the administration of an antibody or protein which binds to the residues of IRS-1 which are phosphorylated in response to activation of the insulin receptor.

Claim 25 has been canceled. With respect to claim 23 and those claims that depend from claim 23, the claims have been amended to require specific dominant-negative IRS-1 mutants. Claims 39 and 41 now require specific non-protein compounds, e.g., EB1089, that inhibit tyrosine phosphorylation of IRS-1

Applicants submit that the scope of the amended claims is commensurate with the teachings of the specification and therefore request withdrawal of this amendment.

III. Rejections under 35 U.S.C. § 102

Claims 23, 24, 42, 44, 46, and 49 were rejected for anticipation by Tanaka et al., who allegedly describe mutants of IRS-1 that are dominant negative and inhibit signal transduction of the IRS pathway.

Independent claim 23 has been amended to require the step of identifying a mammal that has an elevated level of HAAH compared to a normal nonneoplastic level of the protein. Tanaka et al. fail to describe identification of this treatment cohort. Therefore, the amended claims are not anticipated by Tanaka et al.

Claims 22, 24, 39, 40, and 42 were rejected for anticipation by Morris as evidenced by Rozen et al. In item 13 of the Office Action, the Examiner states:

> Morris et al., disclose a method for inhibiting liver cancer comprising the administration of vitamin D analogs such as EB1089 (page 5, line 29 to page 6, line 27). It is inherent in the method of Morris et al that the vitamin D analog inhibits signal transduction through the IRS signaling pathway.

Although Morris does describe vitamin D analogs and liver tumors, Morris does not describe identification of a mammal having an elevated level of HAAH. Therefore, the amended claims are not anticipated by Morris.

IV. Rejections under 35 U.S.C. § 103

Claims 23, 24, 42, 44, 46, 49, 50, and 51 were rejected for obviousness over Tanaka et al. in view of what was suggested by the reference. In support of the rejection, the Examiner states:

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to mutate positions 897 and 1180 of IRS-1. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings of Tanaka et al on the specific binding sites for downstream effector molecules in IRS-1 signaling. (Item 15 of the Office Action)

The claims have been amended to overcome the *prima facie* determination of obviousness. As was discussed above, independent claim 23 now requires identification of a very specific target population of subjects to which IRS mutants are administered. Tanaka et al. do not describe HAAH, nor do they describe identifying a specific subset of individuals characterized by elevated HAAH levels compared to normal control levels. Thus, Applicant submits that this rejection should be withdrawn.

Claims 23, 24, 39, 40-42 and 44 were rejected for obviousness over Morris in view of Ogawa et al. and Rozen et al. In item 16 of the Office Action, the Examiner stated:

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute wortmannin for EB1089 in the method of treating liver cancer as taught by Morris. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Rozen et al. on the inhibition of IRS-1 phosphorylation by EB1089 and the teachings of Tanaka on the inhibition of tumor growth by dominant negative mutant[s] which lack residues for phosphorylation and downstream signalling. One of skill in the art would conclude that wortmannin would inhibit downstream signaling of IRS-1 phosphorylation, and that said inhibition would be efficacious in the treatment of liver cancer as EB1089 also inhibits downstream signaling of the IRS-1 molecule by inhibiting phosphorylation of said molecule.

None of the cited references describe or suggest HAAH, nor do they describe or suggest any link whatsoever between HAAH and the IRS signalling pathway. The inventors were the first to discover a connection between HAAH and IRS-1, discovering that HAAH is a downstream effector in IRS-mediated signal transduction. The amended claims reflect this surprising discovery by requiring a determination of elevated HAAH levels to identify subjects to which inhibitors of IRS-1

phosphorylation are to be administered. Therefore, amended independent claims 23, 39, and 42 (and those claims that depend from claims 23, 39, and 42) are nonobvious over the cited combination of references. Withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicants submit that the application is in condition for allowance and such action is respectfully requested.

A petition for extension of time and a check in the amount of $ 930.00 is enclosed to cover the petition fee for a three month extension of time pursuant to 37 C.F.R. § 1.17(a)(3). The Commissioner is hereby authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No.21486-032 DIV3.

Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

IABeattie

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Dated: August 26, 2003

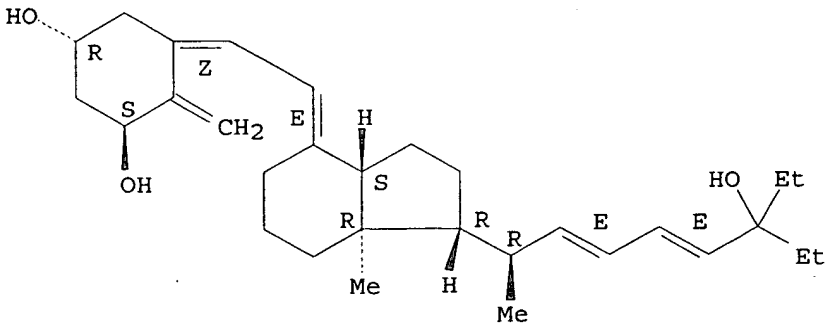
TRA 1826146v1

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 134404-52-7 REGISTRY
CN 1,3-Cyclohexanediol, 5-[(2E)-[(1R,3aS,7aR)-1-[(1R,2E,4E)-6-ethyl-6-hydroxy-1-methyl-2,4-octadienyl]octahydro-7a-methyl-4H-inden-4-ylidene]ethylidene]-4-methylene-, (1R,3S,5Z)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,3-Cyclohexanediol, 5-[[1-(6-ethyl-6-hydroxy-1-methyl-2,4-octadienyl)octahydro-7a-methyl-4H-inden-4-ylidene]ethylidene]-4-methylene-, [1R-[1α(1R*,2E,4E),3aβ,4E(1R*,3S*,5Z),7aα]]-
OTHER NAMES:
CN EB 1089
CN **Seocalcitol**
FS STEREOSEARCH
MF C30 H46 O3
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, DDFU, DRUGNL, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, PHAR, PROMT, RTECS*, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)

Ring System Data

Elemental Analysis EA	Elemental Sequence ES	Size of the Rings SZ	Ring System Formula RF	Ring Identifier RID	RID Occurrence Count
C6	C6	6	C6	46.150.1	1
C5-C6	C5-C6	5-6	C9	333.70.1	1

Absolute stereochemistry.
Double bond geometry as shown.



Calculated Properties (CALC)

PROPERTY (CODE)	VALUE	CONDITION	NOTE
Bioconc. Factor (BCF)	178433	pH 1	(1) ACD
Bioconc. Factor (BCF)	178433	pH 4	(1) ACD
Bioconc. Factor (BCF)	178433	pH 7	(1) ACD
Bioconc. Factor (BCF)	178433	pH 8	(1) ACD
Bioconc. Factor (BCF)	178400	pH 10	(1) ACD
Boiling Point (BP)	608.5+/-45.0 deg C	760.0 Torr	(1) ACD
Enthalpy of Vap. (HVAP)	103.69+/-6.0 kJ/mol		(1) ACD

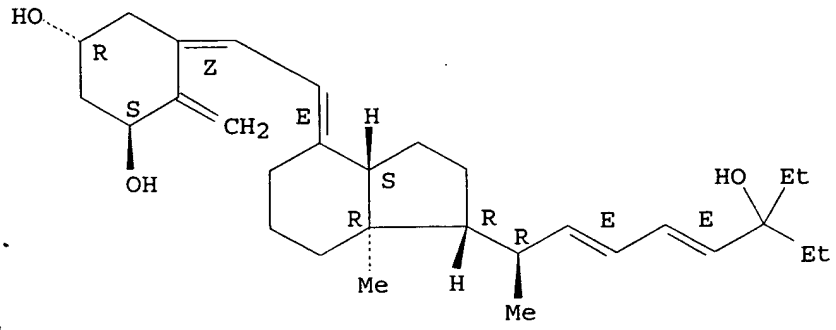
Flash Point (FP)	252.3+/-42.0 deg C		(1) ACD
H acceptors (HAC)	3		(1) ACD
H donors (HD)	3		(1) ACD
Koc (KOC)	199666	pH 1	(1) ACD
Koc (KOC)	199666	pH 4	(1) ACD
Koc (KOC)	199666	pH 7	(1) ACD
Koc (KOC)	199666	pH 8	(1) ACD
Koc (KOC)	199629	pH 10	(1) ACD
logD (LOGD)	7.21	pH 1	(1) ACD
logD (LOGD)	7.21	pH 4	(1) ACD
logD (LOGD)	7.21	pH 7	(1) ACD
logD (LOGD)	7.21	pH 8	(1) ACD
logD (LOGD)	7.21	pH 10	(1) ACD
logP (LOGP)	7.214+/-0.383		(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 1	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 4	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 7	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 8	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 10	(1) ACD
Molecular Weight (MW)	454.68		(1) ACD
pKa (PKA)	13.98+/-0.40	Most Acidic	(1) ACD
Vapor Pressure (VP)	2.40E-17 Torr	25.0 deg C	(1) ACD

(1) Calculated using Advanced Chemistry Development (ACD) Software Solaris V4.67 ((C) 1994-2003 ACD)

180 REFERENCES IN FILE CA (1937 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
180 REFERENCES IN FILE CAPLUS (1937 TO DATE)

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
IN 1,3-Cyclohexanediol, 5-[(2E)-[(1R,3aS,7aR)-1-[(1R,2E,4E)-6-ethyl-6-hydroxy-1-methyl-2,4-octadienyl]octahydro-7a-methyl-4H-inden-4-ylidene]ethylidene]-4-methylene-, (1R,3S,5Z)- (9CI)
MF C30 H46 O3

Absolute stereochemistry.
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT